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FORMULATIONS OF 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE

This application claims priority to U.S. Provisional Application No. 61/179,678, filed May 19, 2009, the entirety of which is incorporated herein by reference.

1. FIELD

Provided herein are formulations and dosage forms of pomalidomide, i.e., 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione or CC-4047. Methods of using the formulations and dosage forms are also provided herein.

2. BACKGROUND

Drug substances are usually administered as part of a formulation in combination with one or more other agents that serve varied and specialized pharmaceutical functions. Dosage forms of various types may be made through selective use of pharmaceutical excipients. As pharmaceutical excipients have various functions and contribute to the pharmaceutical formulations in many different ways, e.g., solubilization, dilution, thickening, stabilization, preservation, coloring, flavoring, etc. The properties that are commonly considered when formulating an active drug substance include bioavailability, ease of manufacture, ease of administration, and stability of the dosage form. Due to the varying properties of the active drug substance to be formulated, dosage forms typically require pharmaceutical excipients that are uniquely tailored to the active drug substance in order to achieve advantageous physical and pharmaceutical properties.

Pomalidomide, which is also known as CC-4047, is chemically named 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pomalidomide is an immunomodulatory compound that inhibits, for example, LPS induced monocyte TNF α , IL-1 β , IL-12, IL-6, MIP-1, MCP-1, GM-CSF, G-CSF, and COX-2 production. The compound is also known to co-stimulate the activation of T-cells. Pomalidomide and method of synthesizing the compound are described, e.g., in U.S. Pat. No. 5,635,517, the entirety of which is incorporated herein by reference.

Due to its diversified pharmacological properties, pomalidomide is useful in treating, preventing, and/or managing various diseases or disorders. Thus, a need exists as to dosage forms of pomalidomide having advantageous physical and pharmaceutical properties.

3. SUMMARY

Provided herein are pharmaceutical dosage forms of pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, hydrate, or clathrate thereof. Also provided herein are methods of treating, managing, or preventing diseases and conditions such as, but not limited to, cancer, pain, Macular Degeneration, a skin disease, a pulmonary disorder, an asbestos-related disorder, a parasitic disease, an immunodeficiency disorder, a CNS disorder, CNS injury, atherosclerosis, a sleep disorder, hemoglobinopathy, anemia, an inflammatory disease, an autoimmune disease, a viral disease, a genetic disease, an allergic disease, a bacterial disease, an ocular neovascular disease, a choroidal neovascular disease, a retina neovascular disease, and rubeosis, using pomalidomide, or a pharmaceutically acceptable stereoisomer,

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prodrug, salt, solvate, hydrate, or clathrate thereof, in the dosage forms described herein.

3.1. Definitions

As used herein and unless otherwise indicated, a composition that is “substantially free” of a compound means that the composition contains less than about 20 percent by weight, more preferably less than about 10 percent by weight, even more preferably less than about 5 percent by weight, and most preferably less than about 3 percent by weight of the compound.

As used herein and unless otherwise indicated, the term “stereomerically pure” means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80 percent by weight of one stereoisomer of the compound and less than about 20 percent by weight of other stereoisomers of the compound, more preferably greater than about 90 percent by weight of one stereoisomer of the compound and less than about 10 percent by weight of the other stereoisomers of the compound, even more preferably greater than about 95 percent by weight of one stereoisomer of the compound and less than about 5 percent by weight of the other stereoisomers of the compound, and most preferably greater than about 97 percent by weight of one stereoisomer of the compound and less than about 3 percent by weight of the other stereoisomers of the compound.

As used herein and unless otherwise indicated, the term “enantiomerically pure” means a stereomerically pure composition of a compound having one chiral center.

As used herein, unless otherwise specified, the term “pharmaceutically acceptable salt(s),” as used herein includes, but is not limited to, salts of acidic or basic moieties of thalidomide. Basic moieties are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that can be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions. Suitable organic acids include, but are not limited to, maleic, fumaric, benzoic, ascorbic, succinic, acetic, formic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, oleic, tannic, aspartic, stearic, palmitic, glycolic, glutamic, gluconic, glucaronic, saccharic, isonicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, benzenesulfonic acids, or pamoic (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate) acids. Suitable inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, or nitric acids. Compounds that include an amine moiety can form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Chemical moieties that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts are alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, or iron salts.

As used herein, and unless otherwise specified, the term “solvate” means a compound provided herein or a salt thereof, that further includes a stoichiometric or non-sto-